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Table of Contents

Page

Chapter One 1

Introduction 1

Purpose of the Study 4

Definition of Terms 5

Significance of the Study 5

Chapter Two 7

Review of the Literature 7

Etiology of Anemia in the Critically Ill 7

Anemia of Chronic Disease 7

Phlebotomy Losses 8

Treatment Options for Anemia in the Critically Ill 11

Incidence of Blood Transfusions in the Critically Ill 12

Reasons for Blood Transfusions in the Critically Ill 14

Current Blood Transfusion Guidelines 16

Risks of Blood Transfusion 21

Immunosuppression 21

Infection 22

Surgical Complications 23

Other Risks 24

Costs of Blood Transfusions 25

Summary 26

Chapter Three 28

Method 28

Design 28

Sample 29

Data Collection Protocol 29

Data Analysis 30

Ethical Considerations 31

Chapter Four 32

Findings 32

Description of the Sample 32

Phlebotomy Practices 34

Course of Anemia 36

Blood Transfusion Practices 37

Association Between Anemia, RBCs Transfusions and Length of Stay 41

Chapter Five 44

Discussion of Findings 44

Anemia 44

RBCs Transfusions 45

Limitations of the Study 47

Implications of the Findings 47

Conclusion 49

References 51

Appendix A 58

Appendix B 59

Appendix C 60

Appendix D 62

Appendix E 64

List of Tables

		Page
Table 1	Subject Characteristics	33
Table 2	Phlebotomy Practices	34
Table 3	RBCs Transfusion Practices	39
Table 4	Indications for RBCs Transfusions	40
Table 5	RBCs Transfusions Based on Admission Diagnosis	41

List of Figures

Page

Figure 1 Mean Number of Blood Draws Per Patient Per Day 35

Figure 2 Mean Phlebotomy Blood Loss Per Patient Per Day 35

Figure 3 Mean Phlebotomy Discard Volume Per Patient Per Day 36

Figure 4 Mean Hemoglobin Per Patient Per Day 37

Figure 5 Mean RBCs Transfusions Per Day 38

Figure 6 Number of Patients Who Received RBCs Transfusions Per Day 38

CHAPTER ONE

Introduction

Nearly 75% of critically ill patients develop anemia in the Intensive Care Unit (ICU) (Parillo, 2001). Among the many causes of anemia in the critically ill are blood loss through phlebotomy and surgical procedures, decreased production of endogenous erythropoietin, and immune associated functional iron deficiency (Vincent et al., 2002). Phlebotomy for diagnostic testing is a major source of blood loss in critically ill patients (Brown & Whalen, 2000). Smoller and Kruskall (1986) reported mean daily blood losses of 41.5 mls, with patients in the ICU having phlebotomy twice as often, and about 3 times more blood drawn daily, than patients outside the ICU. Corwin, Parsonnet, and Gettinger (1995) found that 142 patients with ICU stays more than one week had an average of 61-70 mls/day of blood drawn for diagnostic testing. With a mean stay of 19.6 days, this loss amounted to nearly a litre of blood per patient. According to Tan and Lim (2001), in patients who stay more than a week in the ICU, the equivalent of 30% of the total blood transfused is phlebotomised. Recently however, technical improvements in diagnostic measurements and restraints in blood sampling, have resulted in less blood loss through phlebotomy, and resultant iatrogenic anemia (Von Ahsen, Muller, Serke, Frei, & Eckardt, 2001; Zimmerman, Seneff, Sun, Wagner, & Knaus, 1997). However, volume of iatrogenic blood loss and incidence of iatrogenic anemia vary as institutional practices vary.

Anemia is usually treated with blood transfusions. More than 50% of all patients admitted to the ICU receive at least one unit of red blood cells (RBCs) during their

stay to correct anemia and maintain hemoglobin and hematocrit levels greater than 100 g/L and 30%, respectively (Pohlman, Carven, & Lindsay, 2001). This 10/30 rule, first proposed in 1942 by Adams and Lundy, has become accepted over the years as the transfusion trigger (Surgenor, Hampers, & Corwin, 2001). Historically, physicians have assumed that anemia was risky, particularly among patients with cardiovascular disease, and that transfusion was beneficial for patients with anemia. However, recent data, such as the TRICC trial by The Transfusion Requirements in Critical Care group, suggested that lower levels of hemoglobin are well tolerated in most critically ill patients, including those with cardiovascular disease (Hebert et al., 2001; Hebert et al., 1999). Therefore, it has been advocated that automatic transfusion thresholds be abandoned in favour of a practice of blood transfusion only for defined physiologic need (Hebert et al., 1998; Pohlman et al., 2001; Surgenor et al., 2001). The importance of abandoning specific transfusion triggers in making decisions, particularly in patients with hemoglobin levels greater than 70 g/L, has also been stressed. Guidelines have also recommended that red blood cells be administered one unit at a time with consideration of factors such as age, disease severity, and specific diagnoses (Canadian Medical Association, 1997; Hebert et al., 1998). However, in a recent survey of physicians' transfusion practices with critically ill patients in the United Kingdom, Boralessa et al. (2002) found a reported blood transfusion trigger of 90-100 g/L. This was similar to the findings of Hebert et al. (1998). In another recent study evaluating transfusion practices in European ICUs, 2 years after the TRICC study was published, the mean hemoglobin level, before transfusion among patients who were not actively bleeding, was 85 g/L (Vincent et al., 2002). This is similar to

the findings by Corwin and colleagues (2002) where the mean pre-transfusion hemoglobin was also 85 g/L.

These studies suggest that clinicians have not incorporated the results from the TRICC trial into practice (Carson, 2002), and that despite such recommendations, there is variation in clinical practice among critical care physicians (Hebert et al., 1998; Pohlman et al., 2001; Surgenor et al., 2001). Therefore, perhaps unnecessary RBC transfusions are continuing to occur in critically ill patients. In a recent report by the Canadian Blood Services National Liaison Committee (April, 2002), the executive staff have predicted an increased demand by 7.4% for red blood cells, with Alberta being one of the leading provinces in usage. They have called for a reevaluation of the current system of blood transfusion practice, including the system of funding. Recent concerns regarding the safety of the blood supply and the increasing costs associated with transfusion therapies have also led to a reevaluation of the clinical practices of blood transfusion and blood conservation. A call to action in improving blood transfusion practices and reducing anemia in ICU has also been made by the Canadian Collaborative Improvement Associates group that seeks to improve patient care and safety in the ICUs across Canada (Institute for Healthcare Improvement, 1999). Audits of a facility's blood conservation and transfusion practice may improve the efficiency and appropriateness of anemia management (Goodnough, Brecher, Kanter, & AuBuchon, 1999). Therefore, this prospective observational study was designed to examine the blood transfusion practices, and to determine the relationship between phlebotomy and blood transfusion requirements, in the critically ill in the General Systems ICU of the University of Alberta Hospital.

Purpose of the Study

The objectives of this study were twofold. First, to determine the amount of blood loss through phlebotomy and the incidence of anemia in critically ill adults, and second, to determine the current transfusion practices and indications for RBC transfusions for critically ill adults admitted to the University of Alberta Hospital (UAH) General Systems ICU (GSICU). The specific research questions addressed were:

1. What is the frequency of phlebotomy, per patient, per day, in the UAH GSICU?
2. What is the blood loss in milliliters, via phlebotomy, per patient, per day, in the UAH GSICU?
3. What is the discard-volume, in milliliters, per patient, per day, in the UAH GSICU?
4. What is the incidence of anemia in patients in the UAH GSICU?
5. What is the pre-RBC-transfusion hemoglobin in patients in the UAH GSICU?
6. What is the number of RBC transfusions, per patient, in the UAH GSICU?
7. What is the number of units of RBCs, per transfusion, per patient, in the UAH GSICU?
8. What are the reported indications for RBC transfusions, for patients in the UAH GSICU?
9. What is the association between RBC transfusion and ICU length of stay in patients in the UAH GSICU?
10. What is the association between anemia and RBC transfusions in patients in the UAH GSICU?

11. What are the factors associated with anemia and/or RBC transfusions in patients in the UAH GSICU?

Definition of Terms

Arterial/Central line: an intravascular catheter placed in an artery or large central vein, used for blood collection, among other purposes.

Phlebotomy: blood collected, via veni-puncture or through invasive arterial or venous catheters, for diagnostic tests.

Anemia: hemoglobin level < 120 g/L for women, and <140 g/L for men (Brown & Whalen, 2000)

Discard-volume: the volume of blood and saline mixture in millilitres withdrawn initially from intravascular access lines and discarded to clear the lines, prior to uncontaminated blood collection.

Pre-RBC transfusion hemoglobin: hemoglobin level within three hours prior to blood transfusion.

Red Blood Cells: red blood cells are prepared from whole blood by sedimentation or centrifugation, and are stored at 1-6 degrees Centigrade in citrate-phosphate-dextrose-dextrose anticoagulant. It is then filtered to reduce leukocytes. After removal of most of the plasma, the additive solution, adenine saline 3 (Nutricel) is mixed with the leukocyte reduced red blood cells. The volume of blood ranges from 250-350 mls, and the hematocrit ranges from 50% to 80% (Canadian Blood Services, 1999).

Significance of the Study

Laboratory testing is an important part of patient management in the ICU, providing information in the diagnosis of disease, response to treatment, and

furthering understanding of health and disease (Miller, 1999). However, it has become an important cause of anemia in critically ill patients (Corwin, 2001). Treatment of anemia in the ICU involves blood transfusions. However, blood is a scarce and expensive commodity (Goldhill, Boralessa, & Boralessa, 2002). The donor population is constantly changing, and aging, and the screening process evolving, with new diseases and mutations of older diseases continually threatening the system. However, for critically ill patients, the risk of immunomodulatory effects associated with blood transfusion is greater than blood transmitted infections (Brown & Whalen, 2000). Leukocyte reduction of transfused RBCs has been associated with a significant reduction in infection rates; however, considerable expense is involved, and health care economics are sure to affect transfusion practices. The best way to manage the costs and risks of transfusion, and avoid blood shortages, is to limit blood loss and adopt a conservative approach to blood transfusion (Goodnough et al., 1999). However, despite established findings such as in the TRICC trial by Hebert and colleagues (1999) regarding effectiveness of a restrictive transfusion strategy, variations in blood transfusion practices exist amongst critical care physicians and institutions (Khanna, Hebert, & Fergusson, 2003).

Evaluation of phlebotomy related blood loss and its relation to anemia is not only important for the purposes of reducing or eliminating blood transfusion related risks, but also for reducing unnecessary laboratory testing, which contributes to the expenses of health care facilities. Documenting indications for transfusions has also been shown to improve compliance with guidelines for RBCs transfusion, and becomes a strategy to reduce the number of transfusions (Goodnough, et al, 1999).

CHAPTER TWO

Literature Review

Etiology of Anemia in the Critically Ill

Anemia is defined as a reduction in the hemoglobin level or the number of circulating red blood cells (Pohlman et al., 2001). Normal hemoglobin levels are between 120 g/L and 160 g/L for women and 140 g/L and 180 g/L for men (Brown & Whalen, 2000). The hematocrit- the proportion of red blood cells in the total volume of blood- can also determine if a patient is anemic. A normal hematocrit value ranges from 37% to 48% for women, and 45% to 52% for men (Brown & Whalen, 2000).

Several factors contribute to anemia in the ICU. Insufficient production of red blood cells consistent with anemia of chronic disease, due to bone marrow disease, chemotherapy, nutritional deficiencies, and blunted erythropoietin response, is one factor (Pearl & Pohlman, 2002; Pohlman et al., 2001; Parillo, 2001); blood loss through numerous blood draws, occult gastrointestinal bleeding, and invasive or surgical techniques is another factor.

Anemia of Chronic Disease

Anemia in the critically ill is an under production anemia, what is commonly referred to as the anemia of chronic inflammatory disease (Corwin, 2000). More than 90% of ICU patients have low serum iron, a total iron binding capacity (TIBC), and a serum iron/TIBC ratio but do have a normal, or more usually, an elevated serum ferritin concentration (Corwin, 2000). At a time when iron studies are abnormal, serum erythropoietin (EPO) concentrations are only mildly elevated with little evidence of reticulocyte response to endogenous EPO (Parillo, 2001). The blunted

EPO response observed in the critically ill appears to result from the inhibition of the EPO gene by inflammatory mediators such as interleukin-1 alpha, tumor necrosis factor alpha, tumor growth factor beta and interleukin-1 beta (Corwin, 2000). These same inflammatory cytokines directly inhibit red cell production by the bone marrow and may produce the distinct abnormalities of iron metabolism (Tan & Lim, 2001). Thus, anemia of chronic disease is anemia of immune activation in reaction to new foreign antigens (bacteria, parasites, viruses, neoplasms). This reaction involves the production of cytokines that inhibit the action of EPO on bone marrow cells, and the production of EPO by the kidney, thereby producing an underproduction anemia (Brown & Whalen, 2000).

Phlebotomy Losses

A major problem associated with diagnostic blood loss is iatrogenic anemia. Several investigators as early as in the 1970s examined the problem of diagnostic blood loss by quantifying the amount of blood drawn for diagnostic tests. Eyster and Bernene (1973) examined whether episodes of anemia and reticulocytosis were related to blood loss from diagnostic studies on 93 patients in coronary and pulmonary care units. They found that about 40% of the patients with normal hematocrit values on admission to the critical care units became anemic with no observable bleeding other than from diagnostic tests. Reticulocytosis was also present in 78 patients, with the count ranging from $1.7 \pm 0.77\%$ to $3.4 \pm 1.4\%$. In a larger multi-site study, Lanuza and Jennrich (1976) evaluated the amount of diagnostic blood loss for 253 patients in four diagnostic categories (surgical, open heart surgical, medical, and cardiac) from eight ICUs in six different hospitals, and found that total

blood loss was higher for days 1 and 2 than day 3. Mean daily blood loss was 20 mls for surgical and 50 mls for cardiac surgery patients. The total blood loss for specific patient diagnostic categories also differed by hospital because of factors, such as physician orders, personnel drawing the specimens, and laboratory equipment.

Hashimoto (1982) examined whether health care practitioners had made any progress in decreasing diagnostic blood loss since Eyster and Bernene's study 10 years earlier. The author calculated blood loss from diagnostic tests and the number of times blood was obtained in a medical ICU. The mean blood loss per day for patients was 25.8 mls/day (range 9 to 81 mls). The mean number of phlebotomies per day was 2.6.

Smoller and Kruskall (1986) found that extensive phlebotomy for diagnostic testing in ICU patients caused iatrogenic anemia with resultant blood transfusion. Fifty medical/surgical patients and 50 ICU patients who spent all or part of their stay in CCU, surgical or medical ICUs were studied retrospectively to compare the number of times blood was obtained, the daily blood loss, and the total blood loss. They found that patients in the CCU and ICU underwent more frequent blood tests and lost more blood on a daily basis than general medical/surgical patients. Mean times blood obtained was 1.1 for the medical/surgical patients and 3.4 for the CCU/ICU patients ($p<0.001$). Mean blood loss was 12.4 ml/day for the surgical/medical patients and 41.5 mls/day for the CCU/ICU patients ($p<0.001$). Mean total blood loss was 175 mls for the medical/surgical patients and 762.2 mls for the CCU/ICU patients ($p<0.001$).

Ellstrom (1989) did a retrospective study and quantified the blood drawn by phlebotomy from 28 patients in a respiratory ICU, by measuring the amount drawn for diagnostic tests and adding it to the patients' blood loss from discard volume. The mean daily blood loss was 102 mls (range 5 to 320 mls). Arterial blood gas studies, the most frequently obtained diagnostic test (13 times/day), accounted for a daily mean volume of 39 mls, or 38% of the total volume.

Tarpey and Lawler (1990) investigated the daily and total blood losses for 26 critically ill patients in conjunction with patient acuity. A retrospective chart review for blood loss per day, volume of transfusion, APACHE II scores, and presence of intravascular catheters, were recorded. Mean blood loss for the first 24 hours was 85.3 mls (range 33 to 127 mls). Mean blood loss per day was 66.1 mls, and total blood loss was 336 mls. Mean transfusion volume was 1934 mls for 11 patients. Patients with arterial lines had a mean blood loss of 480 mls, while those without arterial lines lost 105.8 mls ($p<0.01$).

Dale and Pruett (1993) studied 99 patients in a medical ICU and 14 patients on a medical unit to determine phlebotomy blood loss volume. The mean total blood loss was 208 mls (range 10 to 1160 mls) for general medical patients and 550 mls (range 50 to 2500 mls) for patients in the medical ICU. The researchers attributed this to differences in patient acuity and length of stay, although these factors were not analyzed. They also found that patients in the medical unit had 1.5 blood draws per day, a mean blood loss of 208 mls/stay, and a mean of 42 diagnostic tests compared to the ICU patients, who had 3 blood draws per day, a mean blood loss of 550 mls/stay, and a mean of 125 diagnostic tests.

von Ahsen et al. (2001) and Ba et al. (2003) found that the total amount of blood samples drawn for laboratory analysis was lower than in the studies done previously. von Ahsen et al. found the volume of diagnostic blood loss ranged from 41 mls to 20 mls as the length of stay in ICU progressed, and Ba et al. reported a blood loss of 40 mls per day through phlebotomy. They concluded that the decrease in diagnostic blood loss could be related to the use of bedside laboratory determinants and other technical improvements in analyzers. However, it is not known whether this decrease in diagnostic blood loss is indicative of other ICUs.

Treatment Options for Anemia in the Critically Ill

Understanding the etiology and pathophysiology of anemia in the ICU facilitates choosing an optimal treatment strategy (Parillo, 2001). Correcting nutritional deficiencies via administration of iron, Vitamin B12, and folic acid influence erythropoietic activity and may reduce the incidence of anemia. However, since diagnostic blood loss is a major contributing factor to anemia in the ICU, strategies to reduce such blood loss may decrease the incidence of anemia. This includes blood conservation systems to eliminate discard volumes, use of pediatric blood tubes, timing of blood draws, and elimination of standing orders for laboratory tests (Brown & Whalen, 2000). Blood substitutes such as oxygen therapeutics are another option that could be used to enhance oxygen delivery directly to tissues (Brown & Whalen, 2000). However, problems with release of oxygen at tissue level, and the short half-life of these products do not make these products a satisfactory option. Because serum erythropoietin levels are inappropriately low in critically ill patients, a combination of epoietin alfa, iron, and folate therapy can increase reticulocyte count and serum

transferrin levels (van Iperen et al., 2000). According to Corwin (2001), epoietin alfa can raise the hematocrit levels and reduce by at least 50% the number of red blood cell units transfused. Another option to treat blood loss in surgical ICU patients is through autologous transfusion pre, intra, or post operatively (Brown & Whalen, 2000). Although this is considered the safest therapy for blood loss, this practice is not possible in all critically ill patients. Therefore, the primary treatment of anemia in the ICU has been allogenic blood transfusions.

Incidence of Blood Transfusions in the Critically Ill

Considerable variations in blood transfusion practices exist in health care institutions depending more on physicians than on type of procedure, patient population, or hospital (Mallett, Peachey, Sanehi, Hazlehurst, & Mehta, 2000). Studies reviewing the appropriateness of red blood cell transfusions, based on a variety of criteria, estimate that the proportion of unnecessary transfusions ranges from 4 to 66% (Hebert, Schweitzer, Calder, Blajchman, & Giulivi, 1997). Reasons for this large variability in transfusion practices remain elusive, but clinician practices and attitudes may be entrenched and slow to change. Many clinicians continue to routinely transfuse patients to hemoglobin levels to >100 g/L despite little scientific evidence to support this practice (American Society of Anesthesiologists Task Force on Blood Component Therapy, 1996; Carson et al., 1998; Stehling et al., 1994). The Anemia and Blood Transfusions in Critical Care (ABC) investigators conducted a cross sectional study during a 2-week period in November 1999 to evaluate transfusion practices involving 3534 patients from 146 western European ICUs (Vincent et al., 2002). The overall transfusion rate during the 28-day study period was

42%, with an ICU transfusion rate of 37%. While most transfusions were given within the first week of ICU admission, many transfusions continued to be given throughout the 28-day follow-up period. In patients with ICU length of stay longer than 1 week, 73% received a blood transfusion, with the overall mean pre-transfusion hemoglobin level being 85 g/L.

Hebert et al. (1995) reported that 28% of 4875 patients admitted to 6 tertiary ICUs in Canada received red blood cells. Corwin and colleagues (1995) reported that 85% of patients with an ICU stay of greater than one week received at least one unit of RBCs during their stay. Most of the transfusions in the ICU are not associated with acute blood loss, but rather ICU patients appear to have a constant transfusion requirement of 2-4u/week (Corwin, 2001). In a retrospective analysis conducted at Dartmouth-Hitchcock Medical Centre (Corwin, 2001), 165 (35%) transfusion events were associated with acute blood loss (surgery or active bleeding within 24 hours of a transfusion event). Of the 313 (65%) events for non-acute blood loss, no clinical or physiologic indication for the transfusion could be identified at the time of the event for 40%. An additional 23% of the transfusion events for non acute blood loss were solely based on a hematocrit less than 25%, with no clinical evidence of requiring blood at the time of transfusion. It appeared that the transfusion in many of the patients receiving blood for non-acute reasons was driven by an arbitrary "transfusion trigger", a hematocrit of 27%, rather than a clinical or physiologic need. In 2001, it was reported that approximately 31% of ICU patients receive blood transfusions (Hebert et al., 2001).

According to Corwin and colleagues (2004), RBC transfusion practice has changed minimally in the past decade. In their study where current clinical practice in 284 ICUs in the United States was examined, 44% of patients received at least one unit of RBCs during their ICU stay. Almost 70% of the patients admitted to the ICU developed anemia within 48 hours, with a base-line hemoglobin less than 120 g/L. The mean pre transfusion hemoglobin was 86 g/L.

Reasons for Blood Transfusions in the Critically Ill

The decision to transfuse is usually based on patient factors such as volume status, acuteness of the anemia, severity of symptoms, age, and presence of co-morbid conditions, particularly cardiovascular disease (Sherk, Granton, & Kapral, 2000). Cardiovascular responses to anemia include decreased systemic vascular resistance and blood viscosity, and increased heart rate and cardiac output (Tan & Lim, 2001). Delivery of oxygen to the tissues is decreased at the lowest hemoglobin levels and oxygen consumption is increased (Tan & Lim, 2001). The compensatory mechanisms of increased heart rate and stroke volume increase the demands on the myocardium at a time when the oxygen delivery is decreased. Patients with cardiovascular disease therefore tolerate anemia poorly. Hebert and colleagues (1997) studied 4470 critically ill patients, and found that in patients with cardiac disease there was a trend toward an increased mortality when hemoglobin values were <95 g/L as compared with patients with other diagnoses (55% vs 42%, p=0.09). Patients with anemia, a high APACHE II score (>20) and a cardiac diagnosis had a significantly decreased mortality rate when given 1-3 or 4-6 units of allogenic red blood cells (55%: no transfusions versus 35%: 1-3 units or 32%: 4-6 units, respectively, p=0.01). Adjusted odds ratio (OR)

predicting survival was 0.61 (95% CI, 0.23 to 1.03, p=0.03) after 4-6 units compared with non-transfused anemic patients. In the subgroup with cardiac disease, increased hemoglobin values in anemic patients was associated with improved survival (OR= 0.80 for each 10g/L increase, p=0.012).

Some observable outcomes after transfusions are beneficial to patients: decreased rates of solid organ transplant rejection, reduced rates of repetitive spontaneous abortion, and reduced disease activity in Crohns disease and rheumatoid arthritis (Blumberg & Heal, 1998). A large multi-institutional randomized prospective trial of pre-transplant blood transfusion in renal transplantation reported a 9% (p=0.02) graft survival advantage after 5 years in transfused patients (Opelz, Vanrentergehm, & Kirsta, 1997).

Anemia, with hypovolemia, causes impaired tissue oxygenation, with resultant morbidity and mortality (Greenburg, 1995). Each individual has a minimum hemoglobin value that affords adequate tissue oxygenation for that individual's overall cardiovascular, pulmonary, and metabolic status, and once that threshold is passed, tissue oxygenation becomes an important consideration. Because humans are oxygen dependent, maintenance or restoration of normal DO2 to tissues is of primary importance and should be the primary therapeutic goal of a red cell transfusion. Goal-directed therapy, involving adjustments of cardiac preload, afterload, and contractility to balance oxygen delivery with demand, has been used for severe sepsis and septic shock in the ICU. The Rivers trial (Rivers et al., 2001), found that early intervention for severe sepsis/septic shock included transfusing red blood cells to a hematocrit $\geq$ 30% if the central venous oxygen saturation was less than 70%. In-hospital mortality

was 30.5% in the group assigned to early goal-directed therapy, as compared with 46.5% in the group assigned to the standard therapy (p=0.009). During the study period, patients assigned to the early-therapy group had a higher central venous oxygen saturation (70.4 ± 10.7% vs. 65.3 ± 11.4%), a lower lactate level (3 ± 4.4 vs. 3.9 ± 4.4 mmol/L) and a lower base deficit (2 ± 6.6 vs. 5.1 ± 6.7 mmol/L) ($p \leq 0.02$ for all comparisons).

Current Blood Transfusion Guidelines

Few would argue with red blood cell transfusion in a hemodynamically unstable patient during active bleeding. However, precise indications and threshold for transfusion of blood in other situations remain controversial in the critically ill patient, due to lack of data from controlled trials (Sherk et al., 2000). Near the turn of the century, an association between anemia, anesthesia, and surgery was recognised when physicians observed that surgical patients with hemoglobin levels < 100 g/L did not do well (Greenburg, 1995). Adams and Lundy (1942) recommended the administration of red blood cells for hemoglobin concentrations ranging from 80 to 100 g/L in the perioperative period. Since then, although scientific evidence supporting this approach has been advanced, physicians continue to use 100 g/L (hematocrit of 30%) as a hemoglobin threshold (Hebert et al., 1998). However, prompted by concerns over transfusion related infections, recent guidelines emphasize that the decision to transfuse should not be determined by a single hemoglobin concentration. Yet, surveys of transfusion practices have repeatedly documented the importance attributed to hemoglobin triggers. In the 1980s, 88% of anaesthesiologists surveyed believed preoperative hemoglobin concentrations of 90

g/L to be mandatory (Stehling et al., 1987). Later, Stehling and Esposito (1989) documented that 65% of anaesthesiologists required a preoperative hemoglobin concentration of at least 100 g/L.

Current practice guidelines are based primarily on expert consensus and therefore vary in their recommendations. Guidelines have been published by several organizations including the National Institutes of Health consensus conference on perioperative transfusion of red blood cells, the American College of Physicians, and the Canadian Medical Association (Taylor et al., 2002). These guidelines recommend that blood should not be transfused prophylactically. They suggest that the threshold for transfusion should be a hemoglobin between 70 and 80 g/L in non-critically ill patients. The National Institutes of Health (NIH) suggests a hemoglobin of 70 g/L in perioperative patients, while the American Society of Anaesthesiologists states that RBC transfusion will provide the greatest benefit when the hemoglobin is between 60 and 100 g/L (NIH, 1988; American Society of Anaesthesiologists Task Force on Blood Component Therapy, 1996). Surgenor and colleagues (2001) recommend maintaining hemoglobin levels of 100-120 g/L with red blood cell transfusions to optimize oxygen delivery in patients with cardiovascular disorders. While there is disagreement among experts, there is even more among practicing clinicians. A survey of Canadian intensivists documented transfusion threshold hemoglobin levels ranging from 60 to 120 g/L for the same patient (Hebert et al., 1998).

The majority of existing guidelines for the transfusion of red blood cells and other blood components are derived from animal experiments and observation of patients undergoing resuscitation, surgery, and anaesthesia (American College of Physicians,

1992; American Society of Anaesthesiologists Task Force on Blood Component Therapy, 1996). Since data on the transfusion needs of critically ill patients are scarce, Hebert and colleagues recently addressed this with a series of multicentre studies in Canada (Hebert et al., 1995, 1997, 1999). Such studies suggested that a much lower hemoglobin threshold for red blood cell transfusion (i.e. 70 g/L rather than 100 g/L) was safe practice in critically ill patients.

To evaluate the effects of a restrictive and liberal RBCs transfusion strategy on mortality and morbidity, a multicentre Canadian study on 69 critically ill patients, was done by Hebert and colleagues in 1995. Hemoglobin levels were maintained at 100-120 g/L in the liberal group, and between 70-90 g/L in the restrictive group. APACHE II scores were similar in both groups. The restrictive group received 2.5 RBC units per patient compared with 4.8 units per patient in the liberal group. This represented a 48% decrease in RBC units transfused per patient. The 30-day mortality rate was 24% in the restrictive group compared with 25% in the liberal group. However, this study lacked power to detect small but clinically significant differences. Therefore, a larger multicentre, Canadian, randomized controlled trial was conducted by the same group of investigators.

Hebert and colleagues (1999) did a randomized controlled trial (the TRICC) to determine whether a restrictive strategy of red blood cell transfusion and a liberal strategy produced equivalent results in critically ill patients. The rates of death from all causes at 30 days and the severity of organ dysfunction were compared. Eight hundred and thirty- eight critically ill patients, with euvolemia after initial treatment who had hemoglobin concentrations of less than 90 g/L within 72 hours after

admission to the ICU were enrolled. Four hundred and eighteen patients were randomly assigned to a restrictive strategy of transfusion, in which red blood cells were transfused if the hemoglobin concentration dropped below 70 g/L and hemoglobin concentrations were maintained at 70 to 90 g/L. Four hundred and twenty patients were assigned to the liberal strategy, in which transfusions were given when the hemoglobin concentration fell below 100 g/L and hemoglobin concentrations were maintained at 100 to 120 g/L. Overall, the results showed that the 30 day mortality was similar in the two groups (18.7 % versus 23.3%, p=0.11). However, the rates were significantly lower with the restrictive transfusion strategy among patients who were less acutely ill- those with an APACHE II score of $\leq$20 (8.7% in the restrictive strategy group and 16.1% in the liberal strategy group, p=0.03)- and among patients who were less than 55 years of age (5.7% and 13%, respectively, p=0.02), but not among patients with clinically significant cardiac disease (20.5% and 22.9%, respectively, p=0.69). The mortality rate during hospitalization was significantly lower in the restrictive strategy group (22.2% versus 28.1%, p=0.05). The authors concluded that a restrictive strategy of red blood cell transfusion was at least as effective as and possibly superior to a liberal transfusion strategy in the critically ill, with the exception of patients with acute myocardial infarction and unstable angina. Maintaining hemoglobin concentrations in the range of 70 to 90 g/L decreased the average number of red blood cell units transfused by 54% and decreased exposure to any red cells after randomization by 33%. Red blood cell transfusions used as a means of augmenting oxygen delivery did not offer any survival advantage in patients with normovolemia when hemoglobin concentrations exceeded 70 g/L.

Despite being one of the largest randomized controlled trials that evaluated outcomes in critically ill patients treated with a restrictive transfusion approach, the findings of this study are not widely accepted. Possible reasons may be due to the exclusion criteria of the study, and that only a quarter of the eligible patients was randomized. Patients less than 16 years of age, inability to receive blood products, active blood loss at the time of enrollment, chronic anemia, pregnancy, brain or imminent death, physician decision to possible withdrawal or withholding of treatment, and postoperative cardiac surgical procedures were excluded. Clinicians are therefore hesitant in applying the results in clinical practice. Neurointensivists argue that no subgroup analysis was performed for patients with primary or secondary brain injury (Gemma & Beretta, 1999). Restricting transfusion in these patients may result in a low ratio of cerebral oxygen delivery to cerebral metabolic rate, adversely affecting the outcome after brain injury (Marion, Darby, & Yonas, 1991). Therefore, an optimal hemoglobin concentration is crucial in the struggle to optimize cerebral oxygen delivery in this setting. Others argue that correct statistical methods were not used to evaluate the findings (Ledger, 1999).

In a subgroup of patients with cardiovascular disease from the TRICC trial, Hebert and colleagues (2001) suggested that most hemodynamically stable critically ill patients with cardiovascular disease may be transfused when hemoglobin falls below 70 g/L, and that the hemoglobin concentrations may be maintained between 70 and 90 g/L. In the 357 patients with cardiovascular disease, the 30-day mortality rate was 23% in the restrictive and liberal strategy groups (p=1.00). Sixty-day ICU and hospital mortalities were not significantly different between groups. However, a non-

significant decrease in overall survival rate in the restrictive group was noted in those patients with confirmed ischemic heart disease, severe peripheral vascular disease, or severe co-morbid cardiac disease (p=0.30). The investigators concluded that a restrictive blood transfusion strategy appears to be safe in most critically ill patients with cardiovascular disease, with the exception of patients experiencing acute myocardial infarction or unstable angina.

Risks of Blood Transfusion

Despite benefits, there are significant risks and costs associated with RBCs transfusion. As many as 20% of patients receiving RBCs transfusion may experience some type of adverse event. Risks associated with blood transfusion include immunosuppression, infection, and surgical complications (Brown & Whalen, 2000).

Immunosuppresion

Evidence suggests that allogenic blood alters the immune response in a way that may render the recipient vulnerable to infection, the recurrence of malignancy, or the reactivation of latent viruses (Klein & Weiskopf, 1999). This phenomenon has been termed the immunomodulatory effect of blood transfusion. Numerous alterations in circulating blood cells have been reported in patients transfused with allogenic blood. These changes include decreased numbers of circulating lymphocytes, modifications in the T-cell helper/suppressor ratio, changes in B cell function, down-regulation of antigen presenting cells, and activation of immune cells as measured by a number of cell surface markers (Klein & Weiskopf, 1999). Some of these changes persist for months or even longer after transfusion.

Infection

Manganaro et al. (2000) hypothesized that critically ill patients may be at increased risk for immunosuppressive complications of packed red blood cell transfusion, therefore at increased risk for nosocomial infections in the ICU. Data were collected on 1717 patients admitted to a single medical-surgical ICU. Nosocomial infection rates were compared among three groups: entire cohort, transfusion group, and non-transfusion group, while adjusting for severity of illness, age gender and number of RBCs transfused. Nosocomial infection rate for the entire cohort was 5.94%. Nosocomial infection for the transfusion group (n=416) and non-transfusion group (n=1301) were 15.38% and 2.92%, respectively. The more units of RBCs transfused, the greater the chance of infection, with each unit of RBCs given, the odds of developing an infection increasing by a factor of 1.5.

The risk of Human Immunodeficiency Virus (HIV) from blood transfusion is 1 in 1,800,000, 1 in 1,600,000 for Hepatitis C Virus (HCV), and 1 in 220,000/unit for Hepatitis B Virus (HBV) due to recent introduction of Nucleic Acid Technology (Busch, Kleinman, & Nemo, 2003; Hebert et al, 1997). It is likely that NAT testing for Hepatitis A Virus and Parvovirus B19 nucleic acids will be added to blood donor screening requirements during the next several years (Busch et al., 2003). The 2002 epidemic of West Nile Virus transmission, which included the first documented cases of transfusion and transplant transmission, has led to a major effort to develop and implement West Nile Virus NAT assays by the summer of 2003 (Busch et al, 2003).

A potential blood borne infectious agent present in any region of the world could travel to other countries overnight. This has led to increased concern with transfusion

risk of parasitic agents such as malaria, trypanosoma cruzi, and prions such as vCJD (variant Creutzfeldt-Jakob disease), a fatal degenerative neurological disease. The etiologic agent of vCJD is the same agent that causes bovine spongiform encephalopathy, which has become a major global animal health problem. Although transmission of related prion diseases by blood transfusions has been reported in several animal models, no cases of transfusion transmitted vCJD in humans have been reported anywhere in the world to date (Busch et al., 2003). However, it must be noted that vCJD is a new disease and other transmissible spongiform encephalopathies are known to have long incubation periods, the 6 year observation period from the discovery of the disease is too short to draw any firm conclusions about transfusion related transmissions (Busch et al., 2003).

Surgical Complications

Patients receiving allogenic blood experience greater morbidity, longer hospital stays and higher hospital costs than patients receiving equivalent amounts of autologous blood (Blumberg & Heal, 1998). It has also been known that recipients of perioperative allogenic transfusions have increased rates of postoperative bacteria infections due to an ill-defined immunosuppression mediated by the transfusion of contaminating white blood cells with resultant longer hospital stays (Blumberg & Heal, 1998). A relationship between transfusion and length of stay is demonstrated even after adjustment for the effects of bleeding, anemia, duration of surgery, age, and pre-existing medical co-morbidity. Vamvakas and Carven (1998) found that colorectal cancer surgery patients who received allogenic blood transfusions experienced increased morbidity, hospital stays, and cost.

Other Risks

Correcting the decrease in oxygen delivery from anemia using allogenic RBC transfusion has been hypothesized to help with increased oxygen demands during weaning from mechanical ventilation. However, it is also possible that transfusions hinder the process because aged RBCs may not be able to adequately increase oxygen delivery. Temporarily decreased concentrations of 2,3 di-phosphoglycerate and adenosine triphosphate caused by storage impair RBCs deformability and interfere with the ability of the RBCs to unload oxygen (Surgenor et al., 2001). In a study of septic patients undergoing mechanical ventilation who were resuscitated and transfused with blood stored for longer than 15 days was associated with an increased incidence of splanchnic ischemia (Marik & Sibbald, 1993). This may have been due to microcirculatory occlusion in some organs. Furthermore, transfusion of three units of RBCs caused no acute improvement in oxygen uptake. A later study in a septic rat model showed that although fresh RBCs stored for 1 to 3 days increased systemic oxygen uptake ($p<0.05$), old RBCs stored for 28 days did not improve oxygen uptake (Fitzgerald et al., 1997). Three retrospective clinical studies tested the association between the age of transfused blood and duration of stay in the ICU (Martin, Sibbald, Lu, Hebert, & Schweitzer, 1994) and mortality (Purdy, Tweeddale, & Merrick, 1997; Vamvakas & Carven, 1999). Martin et al. (1994) observed a statistically significant association between the transfusion of blood older than 14 days and increased length of ICU stay ($p=0.003$) in 698 critically ill patients. In patients who received a transfusion, aged blood was the only predictor of increased length of stay ($p<0.0001$).

In survivors, only the median age of blood was predictive of duration of stay ($p<0.0001$). Purdy and colleagues (1997) found a negative correlation ($r = -0.73$) between the proportion of red blood cells of a given age transfused to survivors and increasing age of RBCs. Vamvakas and Carven (1999) noted an adjusted increase of 1% in the risk of postoperative pneumonia in post-operative cardiac surgery patients, per day of average increase in the duration of RBCs storage ($p<0.005$), in transfused patients.

Some of the other risks that are associated with allogenic blood transfusions are hemolytic reactions (acute:1 in 25, 000 units transfused, and delayed:1 in 2500-9000), anaphylaxis (1 in 20,000-50,000), transfusion related acute lung injury, graft versus host disease, congestive heart failure (1 in 100), tumour recurrence, transfusion related acute lung injury, and iron overload (Hebert et al., 1997; Goodnough et al., 1999; Brown & Whalen, 2000). All these risks add to the total costs associated with blood transfusions.

Costs of Blood Transfusions

The adequacy of blood supply is threatened with every discovery of a new infectious agent in humans, as it leads to expanded deferral or screening recommendations, resulting in exclusion of potential donors. Although the ability to close the infectious window periods through new assays exists, there is growing pressure to control the escalating costs of medical care in general and of blood transfusions in particular. Cantor et al. (1998) has placed the cost of transfusing one unit of blood at a comprehensive cancer centre at $270 US, and 2 units of RBCs at a range of $548 to $570, which accounted for direct and indirect fixed costs related to

the transfusion procedure. It must be noted that cancer patients may require more laboratory tests and careful monitoring than the typical patient, thus the increased cost of transfusion. Spence (2002) puts the cost of the first unit of allogenic RBCs transfusion at $500 US, with the cost of subsequent units dropping to $350 US per unit with elimination of the need for a type and screen. These costs reflect only the acquisition of units from the blood bank, and do not include any other components of economic analysis.

In Canada, the cost of administering allogenic RBCs is not passed on to patients directly, and as a result, has no impact on bedside transfusion decisions (Hebert et al, 1997). However, information regarding costs may be extremely relevant when comparing allogenic cells to alternative strategies such as autologous blood programs, use of other oxygen carriers or pharmaceutical interventions. In Canada, the unit cost of in patient allogenic RBCs transfusion ranges from $500 to $1000 (K. Gagliardi, Canadian Blood Services, Ottawa, personal communication, August 18, 2003). The Canadian Blood Services has recently undergone considerable organizational reform, partially motivated by the rising costs of blood products and the perception that the current system has failed to provide incentives for the efficient use of blood products (Wilson & Hebert, 2003). The total expenditures of Canadian Blood Services have risen 51% from an annual total of $422 million in 1998/99 to $638.8 million in 2001/02 (Wilson & Hebert, 2003).

Summary

Anemia is common in the Intensive Care Unit (ICU). Causes of anemia in the ICU are multifactorial. Studies have suggested that blood draws for diagnostic purposes is

a major determinant of anemia in the critically ill. Anemia in the ICU is usually treated with red blood cell transfusion, despite the many risks associated, which are poorly tolerated by the critically ill. Eighty-five percent of patients admitted to the ICU with a length of stay greater than one week are transfused with more than one unit of RBCs (Corwin et al, 1995). Blood transfusion trigger for ICU patients is not known. Also, widely accepted standards for blood transfusion in an ICU do not exist. This is in large part related to difficulties in defining specific transfusion threshold criteria. The TRICC trial by Hebert and colleagues (1999) is a large prospective multicentre Canadian study that suggested a restrictive transfusion policy (hemoglobin level < 70 g/L) showed trends toward better overall outcomes than ICU patients whose transfusion trigger was liberal (hemoglobin < 100 g/L). The results of this trial raise important issues regarding management of anemia in the critically ill. However, blood transfusions continue in the critically ill patient population at different hemoglobin concentrations, while the indications for blood transfusion remain unclear. Considering the varied transfusion guidelines and clinical practice among critical care physicians, and the limitations, risks, and costs associated with blood transfusion in the critically ill, an ongoing review of transfusion practices is essential. Also, a critical evaluation of phlebotomy related blood loss is also important for reducing the incidence of anemia and any transfusions required to replace the blood drawn for diagnostic purposes.

CHAPTER THREE

Method

Design

An observational prospective design was used to gather data regarding transfusion practices in the University of Alberta Hospital General Systems Intensive Care Unit (UAH GSICU) and assess the relationship between phlebotomy blood loss and transfusion practices in critically ill adults of the UAH GSICU. This prospective health record review determined the frequency of phlebotomy, the associated volume of blood loss, the discard volume, and the incidence of anemia in adult patients admitted to the UAH GSICU during the study period. It also determined the incidence of RBCs transfusions, the number of RBCs units per transfusion, the admission hemoglobin, the pre-transfusion hemoglobin, the primary indication for blood transfusion as reported by the attending physician, the association between anemia and RBCs transfusions, and the factors associated with anemia and RBCs transfusions.

The UAH GSICU is a 30-bed adult ICU. It is staffed at any given time by three intensivists, one nurse practitioner, one chief medical resident, 4-6 medical residents, specially trained nurses, nurse educators, along with respiratory therapists, physiotherapists, dieticians, pharmacists, chaplains, social workers, service attendants, and at times, students. The unit does not have a transfusion protocol in place to guide its RBCs transfusion decisions.

Sample

All eligible patients admitted to the UAH GSICU from November to December, 2003 were enrolled in the study. The inclusion criterion was all eligible patients admitted to the ICU during the study period with an arterial or central line. Exclusion criteria were as follows: (a) patients less than 18 years of age, (b) patients who remained in ICU for less than 24 hours, (c) patients with chronic end stage renal disease receiving exogenous erythropoietin, (d) patients who were Jehovah Witness and declined blood products, and (e) patients with confirmed primary hematologic disease, including recent bone marrow transplantation or pancytopenia after chemotherapy.

The UAH GSICU admits approximately 90 patients per month, of which almost 100% have intravascular lines for blood pressure monitoring, colloid or crystalloid infusions, or blood collection. A convenience sample of the first 100 patients admitted during the study period, meeting the inclusion criteria, and agreeing to participate in the study, were included in the study.

Data Collection Protocol

Before the commencement of the study, inservices were held for all registered nurses to ensure they were aware of the study and were familiar with the data collection tools (Appendices A, B, & C). The Medical Director of the ICU informed the physicians of the study through e-mail and/or weekly joint-practice meetings. Informational posters were posted at strategic locations informing staff of the initiation of this study. ICU nurse managers were also reminding/informing the nurses of the study during the daily team meetings prior to each shift.

Eligible patients were identified daily at 0700 AM from the admission roster from the previous night. The researcher then approached the eligible patient or family member to inform them of the study. The data collection sheets were added to the hospital chart of the eligible patient. Sheets A and B were completed by the bedside nurse, and sheet C by the investigator. Sheet A recorded the date and time of blood collection, the discard-volumes, and the total volume of blood drawn for diagnostic purposes. Sheet B recorded blood transfusion events, pre transfusion hemoglobin, number of units transfused per transfusion order, and indication for transfusion as stated by the ordering physician. Sheet C recorded patient demographics such as age, gender, ICU admission date, ICU admission diagnosis, ICU admission hemoglobin, APACHE II score (Appendix E), co-morbidities, and discharge date from the ICU. The data collection sheets were checked daily by the investigator to ensure completion, and missing data was added as necessary. Data was collected until discharge from the ICU or 28 days since ICU admission.

Data Analysis

Descriptive statistics were computed for subject demographics and all study variables. To determine if a relationship existed between phlebotomy blood loss, anemia and RBCs transfusions, Pearson's r was used. Also, to examine relationships existing between age, gender, co-morbidities, APACHE II score, and length of ICU stay on the incidence of anemia and RBCs transfusions, Pearson's r was used. As no bivariate significant variables were identified to determine predictors of anemia and RBCs transfusions, a multivariate logistic regression analysis was not conducted. Level of significance was $p < 0.05$.

Ethical Considerations

Support for the study was obtained from the Regional Director of Critical Care, the Medical Director of UAH GSICU, and the Nursing Director of Critical Care of the University of Alberta Hospital. Ethical approval was obtained from the Health Research Ethics Board, University of Alberta. Once eligible patients were identified, the researcher approached the patient or family member to explain the study and it's purpose, and informed consent was obtained (Appendix D). The patient or family member was informed that allowing access to their health records was voluntary with the opportunity to withdraw at any given time with no consequences to quality of care. They were also informed that standard medical and nursing care would continue to be given, as only data from their health records was recorded. No individual benefits, other than advancement of knowledge related to anemia and blood transfusions in the critically ill, were anticipated from their participation in this study. Subject confidentiality was guaranteed by assigning case numbers, and was identified only by this number during this study period. Data collected remains secure under lock and key in a filing cabinet.

CHAPTER FOUR

Findings

The purpose of this study was to determine the amount of blood loss through phlebotomy, the incidence of anemia, and the current transfusion practices and indications for RBCs transfusions, for critically ill adults, admitted to the University of Alberta (UAH) General Systems Intensive Care Unit (GSICU). A prospective observational design was used to gather data during the study period of November to December, 2003. Descriptive statistics were computed for subject demographics and all study variables. To determine if a relationship existed between phlebotomy blood loss, anemia and RBCs transfusions, Pearson's r was used. Also, to examine relationships existing between age, gender, co-morbidities, APACHE II score, and length of ICU stay on the incidence of anemia and RBCs transfusions, Pearson's r was calculated.

Description of the Sample

There were 110 patients admitted into the UAH GSICU during the data collection period. Four patients did not meet the inclusion criteria, and 2 refused to participate in the study. Phlebotomy, anemia, and blood transfusion data were, therefore, collected on 104 eligible patients. Four patients were excluded from the study, as data were incomplete. Of the 100 patients included, 5 patients were readmitted to the ICU after >72 hours of discharge from the ICU, and were re-enrolled in the study. Table 1 presents the characteristics of the patients on admission to the GSICU. The mean patient age was 56.5 $\pm$14.8 years (range: 18 to 85 years), with 19% (n = 19) older than 70 years of age. Majority of the patients (n = 49) were between 50 to 70 years of

age. Men accounted for 57% of the patients in the study. The most frequent admitting diagnosis was complications related to the respiratory system (41%). Co-morbidities were documented on all study patients; patients with a cardiac history accounted for 16% (n = 16) of the study patients. The mean admission APACHE II score was 15 ± 7, with a range of 3 to 36. The mean admission hemoglobin was 109 g/L ± 22.5 g/L, with a range of 63 g/L to 182 g/L. The mean ICU length of stay was 7.7 ± 6.6 days, with a range of 1 to 28 days. Thirty-five patients (35%) stayed longer than 7 days.

Table 1
Subject Characteristics (N = 100)

Characteristics	*Frequency*	*Characteristics*	*Frequency*
Age		*Co- morbidities*	
18-30 years	7	Liver insufficiency	12
		CAD history	16
31-50 years	25	CHF	3
		HTN	14
51-70 years	49	Diabetes mellitus	8
		COPD	5
71-90 years	19	Chronic renal failure	4
		Other	32
Gender		*Admission Hemoglobin*	
Male	57	60-80 g/L	7
		81-100 g/L	32
		101-120 g/L	32
Female	43	121-140 g/L	22
		141-182 g/L	7
Admission Diagnosis		*Admission APACHE II Scores*	
Neurologic	8	1-20	75
		21-30	21
Cardiovascular	7	>30	4
		Length of Stay	
Respiratory	41	1-3 days	26
Gastrointestinal	17	4-7 days	39
Genitourinary	3	8-12 days	19
Multisystem	9	13-20 days	9
Other	15	21-28 days	7

Phlebotomy Practices

The number and volume of blood samples drawn during patients' stay varied widely (Table 2). A total of 88 patients (88%) had up to 50 phlebotomies, 93 (93%) had up to 100 phlebotomies, and 7 (7%) had more than 100 phlebotomies during their length of stay in the GSICU.

Table 2
Phlebotomy Practices

	Mode	*Median*	*Mean (SD)*	*Range*
Phlebotomy Rate Per Patient				
Per Day	5.3	3.5	3.7 (1.8)	2 - 15
Total LOS	15.0	19.5	29.6 (29.3)	3 - 155
Blood Loss Per Patient (mls)				
Per Day	18.25	22.7	24.7 (10.3)	8 - 59
Total LOS	117.0	156.5	223.6 (183.4)	32 - 944
Phlebotomy Discard Volume Per Patient (mls)				
Per Day	7.7	12.4	13.2 (6.3)	3 - 54
Total LOS	21.0	68.0	106.0 (103.5)	0 - 528

The mean number of phlebotomies per patient was 29.6 $\pm$ 29.3 for the total length of stay, with a mean of 3.5 $\pm$ 1.04 per patient per day. Figure 1 shows the mean number of phlebotomies per patient per day.

The mean blood volume per phlebotomy was 7.6 $\pm$ 6.3 mls. The mean blood loss volume via phlebotomy was 25 $\pm$ 10.3 mls per patient per day, and 223.6 $\pm$ 183.4 mls per patient for the length of stay in ICU. The mean blood loss for all patients was the greatest on the day of admission, averaging 51.4 $\pm$ 17.1 mls, and the least on the day of discharge, averaging 16.6 $\pm$ 11.3 mls. Figure 2 shows the mean phlebotomy blood loss per patient per day.

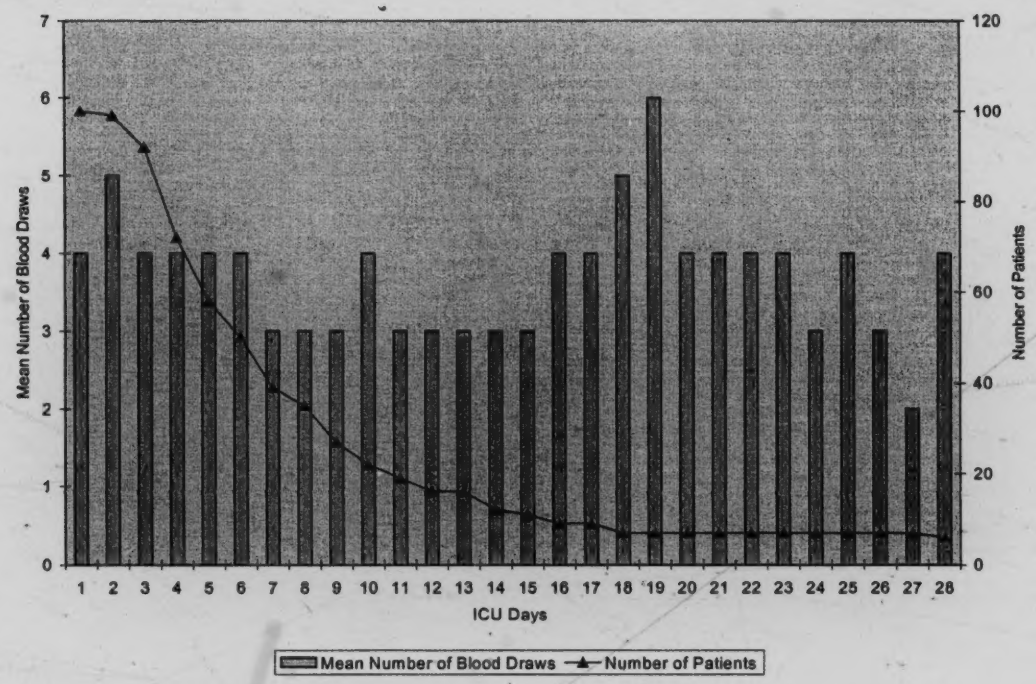

Figure 1. Mean Number of Blood Draws Per Patient Per Day

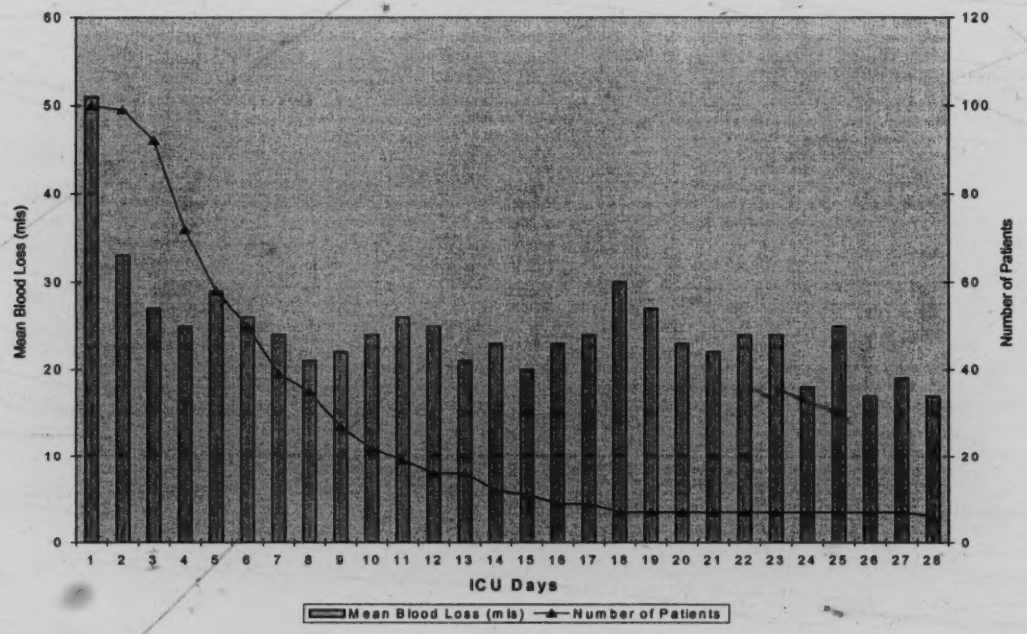

Figure 2. Mean Phlebotomy Blood Loss Per Patient Per Day (mls)

The mean discard volume per patient for total length of GSICU stay was 106.1 ± 103.6 mls, and per day was 3.8 ± 3.7 mls. Mean blood draws, phlebotomy blood loss, and discard volume peaked again around ICU days 17 to 19. Figure 3 shows the mean phlebotomy discard volume per patient per day.

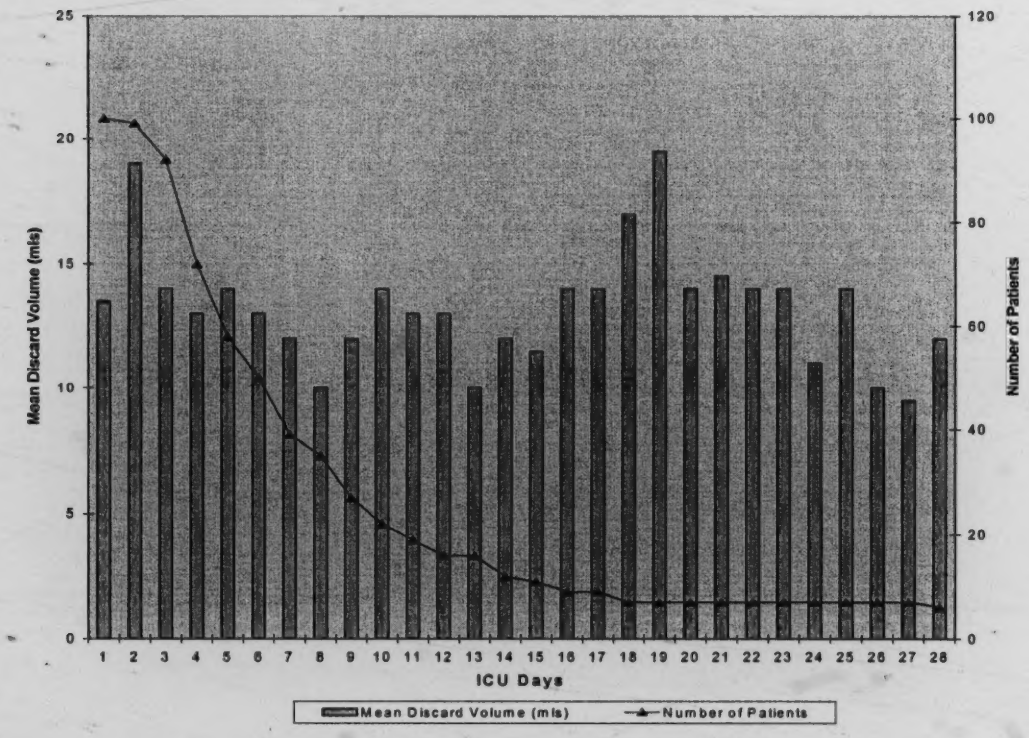

Figure 3. Mean Phlebotomy Discard Volume Per Patient Per Day (mls)

Course of Anemia

The mean admission hemoglobin was 108.8 ± 22.6 g/L, with 71% having an admitting hemoglobin less than 120 g/L, and 39% less than 100 g/L (Table 1). Majority of the patients (n= 86, 86%) were anemic on admission to the GSICU. The overall incidence of anemia during their stay in the ICU was 98%. By ICU day 8, 97% (n = 34) of the patients were anemic, and by ICU day 13, 100% (n = 16) of the

remaining patients were anemic. Figure 4 shows the mean hemoglobin per patient per day.

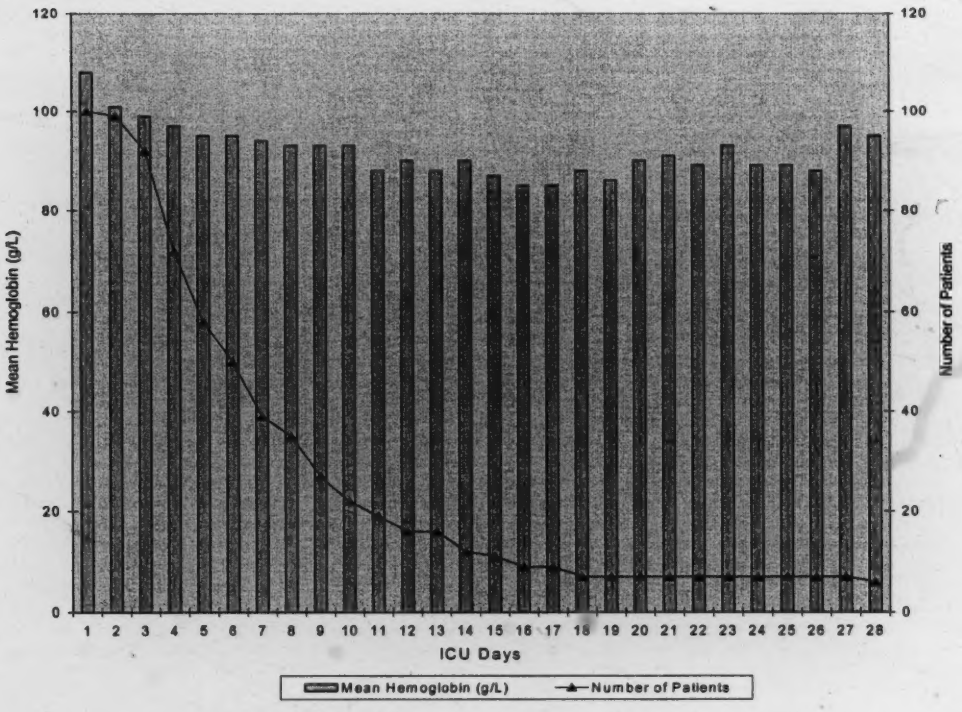

Figure 4. Mean Hemoglobin Per Patient Per Day (g/L)

Blood Transfusion Practices

The mean number of RBCs units transfused per patient per day was 1.5 $\pm$ 0.4 units, for a mean of 1.66 $\pm$ 0.5 units during the total GSICU stay, peaking on ICU days 5 and 27. Figure 5 shows the mean RBCs transfusions per day. The mean number of patients per day who received RBCs transfusions was three. Figure 6 shows the number of patients who received RBCs transfusions per day.

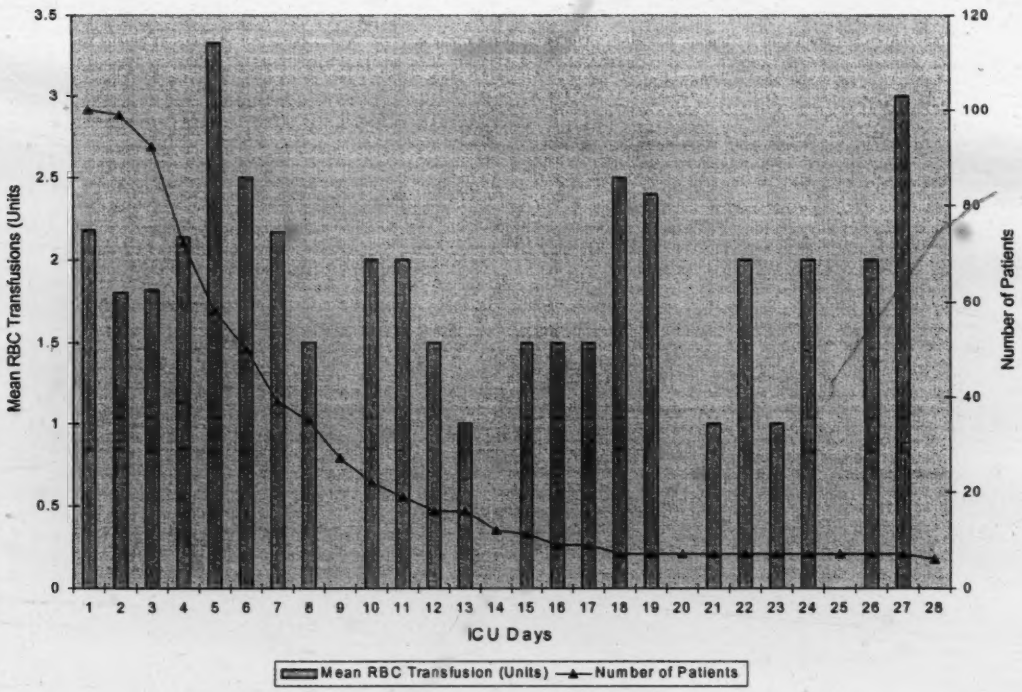

Figure 5. Mean RBCs Transfusions Per Day (Units)

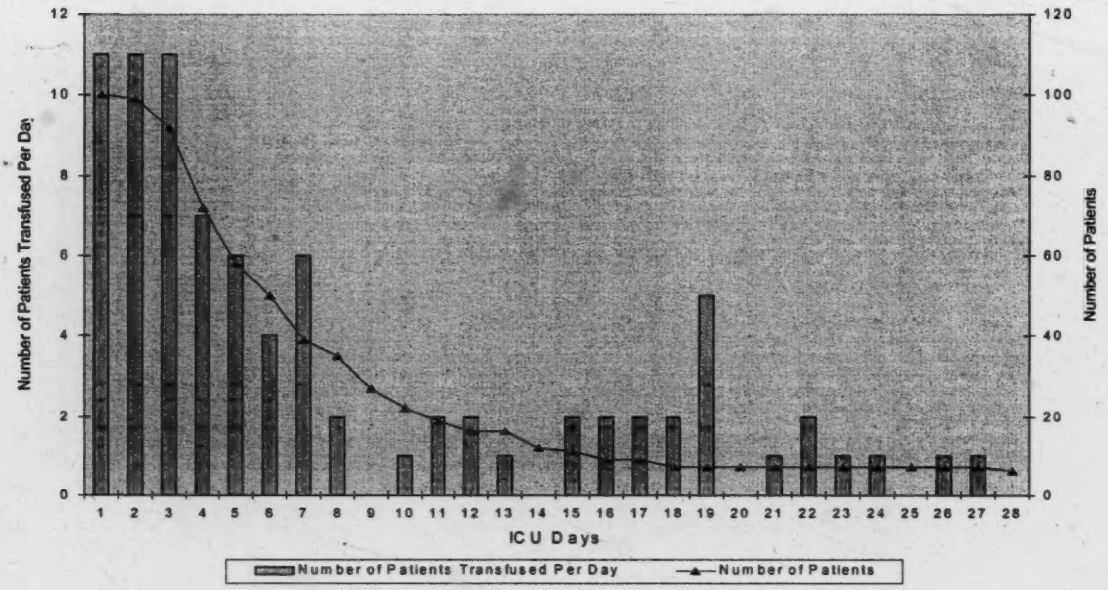
Number of Patients Transfused Per Day
Number of Patients
ICU Days
Number of Patients Transfused Per Day
Number of Patients

Figure 6. Number of Patients Who Received RBCs Transfusions Per Day

The mean number of RBCs units per transfusion order per day was 1.38 ± 0.34 units, and per total GSICU stay was 2 ± 0.5 units. There were 83 RBCs transfusion events during the study period, with a total of 158 RBCs units being transfused (Table 3). Majority of the RBCs transfusion orders were for 2 units per transfusion (n = 52, 630%). The mean pre-transfusion hemoglobin was 73.5 ± 4.7 g/L for this cohort. The mean pre-transfusion hemoglobin was 75 ± 4.1 g/L for those with acute bleeding, and 72 ± 5.4 g/L for those without acute bleeding. Majority of the RBCs transfusions occurred in the pre-hemoglobin range of 71 to 80 g/L (n = 32, 39%), with pre-transfusion hemoglobin concentration exceeding 90 g/L in only 5% (n = 4) of cases.

Table 3
RBCs Transfusion Practices

RBCs Transfusions Per Patient (units)				
	Mode	Median	Mean (SD)	Range
Per Day	1.4	1.5	1.5 (0.4)	1-2
Total Length of Stay	2	2	1.66 (3.25)	0-19
RBCs Units Per Transfusion Order				
	Mode	Median	Mean (SD)	Range
Per Day	1.25	1.4	1.38 (0.34)	1-2
Total Length of Stay	2	2	2 (0.5)	2-2

Pre- Transfusion Hemoglobin (g/L) and Number (Percentage) of Transfusions	
< 60	3 (3.6%)
60-70	29 (35%)
71-80	32 (38.5%)
81-90	15 (18%)
91-100	4 (5%)

Units per Order and Units Transfused		
Units per Order	Frequency (%)	Number of Units
1	26 (31)	26
2	52 (63)	114
3	3 (4)	9
4	1 (1)	4
5	1 (1)	5
Total	83 (100)	158

Patients with a cardiac history were transfused at a hemoglobin of 82 ± 6.5 g/L, giving a transfusion rate of 8%. Table 4 gives the summary of indications for RBCs transfusions.

Table 4
Indications for RBCs Transfusions

Indication for Transfusion	Frequency	Percentage
Anemia	38	46
Acute bleeding	33	40
Cardiac History	7	8
Hypoxemia	3	4
APACHE II	2	2

Patients admitted to the UAH GSICU with respiratory disorders received up to 34% (n = 54) of the transfusions (Table 5). Patients admitted with cardiovascular disorders received 11.5% (n = 18) of the transfusions. The RBCs transfusion rate during the total UAH GSICU stay was 40%, with a daily transfusion rate of 13.6%. Patients whose length of stay was longer than 7 days (n = 28) had an overall transfusion rate of 70%. Transfusion rate was consistent across age groups from 37.5% in patients less than 50 years of age, and 42.5% in those over 50 years of age. There was no difference in the transfusion rate based on gender. Over 39% of all transfused patients received their first RBC transfusion within the first three days in UAH GSICU. The RBCs transfusion rate was 11% (n = 11) at admission, and peaked on ICU day 19 at 71% (n = 5). The mean length of stay of those who received RBCs

transfusions was 11.45 days, and those who did not receive RBC transfusions was 5.2 days.

Table 5
RBCs Transfusions Based on Admission Diagnosis

Number of RBCs units Transfused Based on Admission Diagnosis		
Admission Diagnosis	Number of RBC Units	Percentage
Nervous System	6	4
Cardiovascular System	18	11.5
Respiratory System	54	34
Gastrointestinal System	32	20.25
Genitourinary System	2	1
Multisystem	32	20.25
Other	14	9
Total	158	100

Other blood products such as platelets, plasma, albumin, and cryoprecipitate were transfused to patients during the study period. The rate of transfusion of other blood products was 18% (n = 18) on ICU day 1, and peaked on ICU days 18 and 19 at 43% (n = 3). The was no transfusion of other blood products on ICU day of discharge. The most frequent other blood product transfused was plasma (45%), followed closely by albumin (36%).

Association Between Anemia, RBCs Transfusions, and Length of Stay

Admission hemoglobin levels contributed to the evolution of anemia in the UAH GSICU. Patients with lower admission hemoglobin levels became more anemic as

their length of ICU stay progressed ($r = -0.66$, $p < 0.01$). Patients with lower admission hemoglobin levels were also more likely to stay longer in the UAH GSICU ($r = -0.16$, $p < 0.01$) and had higher admission APACHE II scores ($r = -0.17$, $p < 0.01$). Gender, age, admission diagnoses, comorbidities, or phlebotomy practices did not influence the evolution of anemia in the UAH GSICU.

Severity of illness at time of admission influenced RBCs transfusion rates ($r = 0.24$, $p < 0.05$), with 62% of RBCs transfusions occurring in patients with APACHE II scores of 13 to 24, and 19% in patients with APACHE II scores greater than 25. As patients stayed longer in the UAH GSICU, they received more RBCs transfusions ($r = 0.78$, $p < 0.01$). This may be because patients got more anemic as their length of ICU stay increased. In fact, every patient that received a RBCs transfusion was anemic ($r = 1.0$, $p < 0.01$). There was a significant correlation between RBCs transfusions and phlebotomy practices. As the volume of blood loss increased through increased number of total phlebotomies and resultant discard volumes, the total number of RBCs transfusions also increased ($r = 0.80$, $p < 0.01$). Of those patients who required transfusions, 70% had phlebotomy related blood loss of more than 300 mls for their total GSICU stay, which is equivalent to one unit of RBCs. Patients who received more than 5 units of RBCs during their length of GSICU stay had a mean phlebotomy related blood loss of over 700 mls, and a mean discard volume of 390 mls.

As the length of stay in the UAH GSICU increased, the total number of phlebotomies per patient also increased ($r = 0.94$, $p < 0.01$). With increase in total phlebotomies, the amount of total blood loss through phlebotomy also increased

($r = 0.97$, $p < 0.01$). Age, gender, admission diagnoses, comorbidities, or admission APACHE II scores did not influence the length of stay.

CHAPTER FIVE

Discussion of Findings

A prospective observational design was used to determine the amount of blood loss through phlebotomy, the incidence of anemia, and the current RBCs transfusion practices and indications for transfusions for critically ill adults admitted to the University of Alberta (UAH) General Systems Intensive Care Unit (GSICU). Data were collected on 100 patients admitted to the GSICU during the study period of November to December, 2003. Data analysis included descriptive statistics for subject demographics and all study variables. Pearson's r was used to determine if a relationship existed between phlebotomy blood loss, anemia, and RBCs transfusions. Relationships existing between age, gender, co-morbidities, APACHE II score, length of ICU stay, and the incidence of anemia and RBC transfusions were determined by Pearson's r.

Anemia

For this study, anemia was defined as hemoglobin levels less than 140 g/L for males, and less than 120 g/L for females. Of the 57 males admitted to UAH GSICU during the study period, 52 were anemic on admission; of the 43 females admitted, 36 were anemic on admission. Patients who were anemic on admission to UAH GSICU (n = 86) continued to stay anemic. Of those who were not anemic on admission (n = 14), 10 became anemic as their stay progressed. Patients with lower admission hemoglobin levels stayed longer in the UAH GSICU, likely due to the acuity of their illness. The incidence of anemia in this study was 86% on admission to UAH GSICU, and 100% by ICU day 13. This is similar to the findings in other studies (Vincent et

al., 2002; von Ahsen et al., 1999). A higher incidence of anemia in the ICU setting has been attributed to many factors including frequent phlebotomies, leading to RBCs transfusions (Corwin et al, 1995). In this study, the total amount of blood loss via phlebotomy was nearly 23,000 mls, with the mean blood loss per patient per day of 25 ± 103 mls. There was also a large amount of blood loss as discard volume, used to clear blood from the intravascular catheters and tubing to prevent clotting, totalling over 10,000 mls during the study period. The frequency of phlebotomies was 3 to 4 mean blood draws per patient per day, and peaked to a mean of 6 blood draws per patient per day around ICU day 19. These findings are similar to other studies (Vincent et al, 2002; Corwin et al, 1995). Although the incidence of anemia increased as patients stayed longer in the UAH GSICU, there was no correlation between anemia and phlebotomy blood loss.

Pearl and Pohlman (2002) and Parillo (2001) have documented the impact of nutritional deficiencies, decreased renal function, sepsis, and inappropriately low erythropoietin levels in the critically ill on the incidence of anemia. The percentage of patients who were anemic and received iron in this study was 2%. None received exogenous erythropoietin or folate. Therefore, it is possible that these factors contributed to the evolution of anemia in this cohort.

RBCs Transfusions

The overall RBCs transfusion rate during the 28-day study period was 40%. Patients with ICU stay longer than 7 days had an overall transfusion rate of 70%, with a peak of 71% on ICU day 19. This is similar to findings in other studies (Corwin et al., 2004; Vincent et al., 2002). While most transfusions were given in the first days

of ICU admission, many continued to be given over the ICU stay. The mean number of RBCs units transfused per patient per day was 1.5 ± 0.4 units, for a mean of 1.66 ± 0.5 units during the total GSICU stay. This is less than the findings in other studies (Corwin et al., 2004; Vincent et al., 2002). Physicians continued to order RBCs transfusions at a rate of two RBCs units per order. Of the patients who required RBCs transfusions, 70% (n = 28) had phlebotomy related blood loss of over 300 mls. However, for 43% (n = 12) of these 28 patients, the stated indication for RBCs transfusion was acute bleeding rather than anemia. Therefore, it is not clear whether phlebotomy blood loss or acute bleeding caused a drop in hemoglobin requiring RBCs transfusions. The mean pre-transfusion hemoglobin was 73.5 ± 4.7 g/L for this cohort. The pre-transfusion hemoglobin for patients with a cardiac history was 82 ± 6.5 g/L. These levels are lower than reported in other studies (Corwin et al., 2004; Vincent et al., 2002; Surgenor et al., 2001; Hebert et al., 1998). This may be due to the influence of findings of studies such as the TRICC trial (Hebert et al., 1999). The TRICC trial had determined that maintaining hemoglobin levels between 70 to 80 g/L was as effective as, and possibly superior to, maintaining a hemoglobin level > 100 g/L in the critically ill, with the exception of patients with acute myocardial infarction and unstable angina (Hebert et al., 1999). A sub group analysis of patients with cardiac disease later revealed that maintaining hemoglobin levels in the 70 to 80 g/L in these patients may be equal or superior to higher hemoglobin levels, as long as their APACHE II was <20 or age <55 years (Hebert et al., 2001). In this study, the pre-RBCs transfusion hemoglobin levels were similar for those with and without acute bleeding, suggesting RBCs transfusion decisions were determined by their

hemoglobin levels rather than their clinical status. Gender, age, or co-morbidities did not play a significant role in transfusion decisions.

Limitations of the Study

Physicians and nurses at UAH GSICU were aware that phlebotomy and RBCs transfusion practices were being evaluated, which could have led to a temporary modification of behaviours. There was no validation of the accuracy of the volume of blood drawn by nurses for phlebotomy during this study. Therefore, the volume of blood loss via phlebotomy may be higher than reported in this study. Data on the patient's volume status, incidence of anemia, acute blood loss, RBCs transfusion events, and length of stay in hospital prior to GSICU admission, were not collected in this study. Also, blood loss via hemodialysis filters during GSICU stay was not documented. Also, the effect of transfusion with other blood products on anemia was not analyzed. These factors may have influenced anemia in this cohort. As patients with acute blood loss were not excluded from the study, the overall RBCs transfusion rate may have been increased. Transfusion events in surgical patients did not include red blood cell transfusion events that may have occurred in the operating room. Therefore, the total number of transfusions may be higher than reported in this study.

Implications of the Findings

In this study, anemia was a common occurrence in the critically ill patients admitted to the UAH GSICU, and over a third of the patients received at least one unit of RBCs transfusion. Other studies have suggested similar prevalence of anemia and blood transfusions in the critically ill (Vincent et al., 2002, von Ahsen et al., 1999; Corwin et al., 1995). Because there is increased awareness of the shortage in

blood supply, and the risks associated with RBCs transfusions, there is a strong impetus to devise strategies to reduce the development of anemia in the critically ill. Understanding the etiology and pathophysiology of anemia in the critically ill facilitates choosing optimal treatment strategies. Frequent phlebotomy, acute blood loss, nutritional deficiencies, and a blunted erythropoietin response due to pre-existing chronic illness are a few of the known risk factors for anemia in the critically ill.

In this cohort, there was no significant correlation found between anemia and phlebotomy blood loss, likely due to majority of the patients in this study being anemic. However, phlebotomy blood loss accounted for over 330 mls, inclusive of discard volume, per patient, during their total GSICU stay; this is equivalent to a unit of RBCs. Therefore, strategies to reduce phlebotomy blood loss may be needed to reduce the incidence of anemia. These include using multichannel microchemistry instruments for point-of-care testing, pediatric tubes for blood collection, inline blood conservation devices to eliminate discard volumes, timing and batching of phlebotomies, elimination of routine ICU standing orders for phlebotomies, and daily assessment of frequency of phlebotomies. Documentation of phlebotomy blood loss on the patient's chart by bedside nurses as part of the patient's daily intake/output may also help to identify patients with increased phlebotomy related blood loss. Education and guideline development on blood conservation mechanisms may also be needed.

Only 2% of the patients in this study received oral iron therapy, while none received folate, Vitamin B12, or exogenous erythropoietin. All these are factors in the

evolution of anemia in the critically ill. Nutritional replacements with oral iron and folate should be standard therapy for those patients admitted to the UAH GSICU and are foreseen to have a stay longer than a week. Recent evidence also suggests that treatment with exogenous erythropoietin might be beneficial in increasing reticulocytes and reducing RBCs transfusions in critically ill patients who are foreseen to have an ICU stay longer than 7 days (Corwin et al., 2002).

The overall RBCs transfusion rate in this study was 40%, a finding similar to other studies; however, the overall pre-transfusion hemoglobin was lower than in other studies (Vincent et al., 2002; von Ahsen et al., 1999; Corwin et al., 1995). Although clinical outcomes of patients transfused at lower pre-transfusion hemoglobin levels were not assessed in this study, it is possible that lower hemoglobin levels are tolerated by the critically ill. If that is the case, a lower overall transfusion rate should be aimed for in the future. As a definitive RBCs transfusion protocol is absent at the UAH GSICU, the goal should be to maintain a hemoglobin concentration that maximizes the beneficial effects and minimizes the detrimental effects of RBCs transfusions. An institutional RBCs transfusion protocol that favours a conservative approach to transfusion based on physiological need rather than hemoglobin levels could be developed and implemented.

Conclusion

Anemia occurred in 98% of the critically ill patients admitted to the UAH GSICU, and hemoglobin levels continued to drop with prolonged ICU stay. Over a third of the patients (n = 40) received RBCs transfusions, and 46% of the RBCs transfusions were for anemia. Phlebotomy blood loss is one of the risk factors for development of

anemia in the critically ill. However, in this cohort, despite the large volume of phlebotomy blood loss during the study period, there was no correlation between anemia and phlebotomy practices. However, this does not preclude strategies to reduce phlebotomy related blood loss. Underproduction of erythrocytes due to a blunted erythropoietin response is also a risk factor suggested by others (Corwin et al., 2002) and is seen as a fall in the hemoglobin level during the course of the patient's critical illness (Corwin et al., 2004). Although hemoglobin levels continued to fall during the GSICU stay, it is not known if an inadequate erythropoietin response contributed to anemia in this cohort. There is need for additional studies that identify patients at risk for prolonged ICU stay, and examine the effects of exogenous erythropoietin on their hematopoiesis and RBCs transfusion requirements.

In this cohort, the overall pre-transfusion hemoglobin was 73.5 ± 4.7 g/L, a value lower than reported in other studies. This could be due to the influence of the TRICC trial that suggested a restrictive RBCs transfusion strategy and a lower pre RBCs transfusion hemoglobin. However, the overall RBCs transfusion rate was 40%, a rate similar to other studies. Clinicians also continued to transfuse multiple units at a time. Although knowledge of anemia and blood transfusion has dramatically increased during the past two decades, further studies may be warranted on the evolution of anemia, and the optimal hemoglobin in the critically ill, before change in clinical practice may be seen. Management of anemia and blood transfusion practices in the ICU may need to emphasize the complimentary roles of decreasing phlebotomy related blood loss, increasing RBC production with exogenous hematopoietic agents, and decreasing RBC transfusions by using lower hemoglobin transfusion triggers.

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Appendix A
Data Collection Sheet A

Patient Case Number_____

DATE	TIME	DISCARD VOLUME	TOTAL BLOOD VOLUME (excluding discard)

Appendix B

Data Collection Sheet B

To be filed in by bedside nurse PRIOR to each red cell transfusion event.	Patient case number

Date Time	# of RBC units transfused per order	Pre transfusion Hg:
		☐ ≤ 70 ☐ 71-80 ☐ 81-90 ☐ 91-100 ☐ >100
To be filled in by ordering physician:	**Reason for RBC transfusion:** ☐Age. ☐Disease severity (APACHE II). ☐Acute bleeding. ☐Hypotension. ☐ Hypoxemia. ☐ Acute coronary ischemia. ☐Anemia. ☐Lactic acidosis. ☐Cardiac history ☐Other (specify)_____	
		☐ ≤ 70 ☐ 71-80 ☐ 81-90 ☐ 91-100 ☐ >100
To be filled in by ordering physician:	**Reason for RBC transfusion:** ☐Age. ☐Disease severity (APACHE II). ☐Acute bleeding. ☐Hypotension. ☐ Hypoxemia. ☐ Acute coronary ischemia. ☐Anemia. ☐Lactic acidosis. ☐Cardiac history ☐Other (specify)_____	
		☐ ≤ 70 ☐ 71-80 ☐ 81-90 ☐ 91-100 ☐ >100
To be filled in by ordering physician:	**Reason for RBC transfusion:** ☐Age. ☐Disease severity (APACHE II). ☐Acute bleeding. ☐Hypotension. ☐ Hypoxemia. ☐ Acute coronary ischemia. ☐Anemia. ☐Lactic acidosis. ☐Cardiac history ☐Other (specify)_____	
		☐ ≤ 70 ☐ 71-80 ☐ 81-90 ☐ 91-100 ☐ >100
To be filled in by ordering physician:	**Reason for RBC transfusion:** ☐Age. ☐Disease severity (APACHE II). ☐Acute bleeding. ☐Hypotension. ☐ Hypoxemia. ☐ Acute coronary ischemia. ☐Anemia. ☐Lactic acidosis. ☐Cardiac history ☐Other (specify)_____	
		☐ ≤ 70 ☐ 71-80 ☐ 81-90 ☐ 91-100 ☐ >100
To be filled in by ordering physician:	**Reason for RBC transfusion:** ☐Age. ☐Disease severity (APACHE II). ☐Acute bleeding. ☐Hypotension. ☐ Hypoxemia. ☐ Acute coronary ischemia. ☐Anemia. ☐Lactic acidosis. ☐Cardiac history ☐Other (specify)_____	
		☐ ≤ 70 ☐ 71-80 ☐ 81-90 ☐ 91-100 ☐ >100
To be filled in by ordering physician:	**Reason for RBC transfusion:** ☐Age. ☐Disease severity (APACHE II). ☐Acute bleeding. ☐Hypotension. ☐ Hypoxemia. ☐ Acute coronary ischemia. ☐Anemia. ☐Lactic acidosis. ☐Cardiac history ☐Other (specify)_____	

Appendix C

Data Collection Sheet C

Patient hospital number: _____

Patient case number: _____

Patient age: _____

Patient sex: _____

ICU admission date: _____

ICU admission diagnosis: _____

ICU admission hemoglobin: _____

ICU discharge date: _____

Length of stay in ICU: _____

Other blood products:

☐ yes (specify product, date and time given) _____

☐ no

Folic acid: ☐ yes (specify dosage, date started) _____

☐ no

Iron therapy: ☐ yes (specify dosage, date started) _____

☐ no

Co-morbid conditions (check all that apply):

☐ **Liver insufficiency:** Biopsy proven cirrhosis, documented portal hypertension, episodes of past upper GI bleeding attributed to portal hypertension, prior episodes of hepatic failure / encephalopathy /coma.

☐ **Acute coronary ischemia:** fulfills atleast two of the following:
-complaints of chest pain
-ECG changes
-positive cardiac enzymes.

- ☐ **Cardiac disease:** fulfills atleast one of the following: Angiographically proven CAD disease (one or more vessels with > 50% stenosis), a positive exercise stress test or MI in the year prior to the study, admission to hospital with chest pain or shortness of breath and ECG evidence of cardiac ischemia in the year prior to the study

- ☐ **Congestive heart failure:** NYHA Class IV, chronic restrictive, obstructive or vascular disease resulting in severe exercise restriction, i.e. unable to climb stairs or perform household duties.

- ☐ **Diabetes Mellitus**

- ☐ **Hypertension**

- ☐ **Peripheral vascular disease**

- ☐ **Thromboembolic disease**

- ☐ **Chronic Respiratory Disease:** Documented chronic hypoxia, hypercapnia, secondary polycythemia , severe pulmonary hypertension (> 40 mmHg), or respirator dependency.

- ☐ **Renal:** Receiving chronic dialysis

- ☐ **Immunosuppressed:** The patient has received therapy that suppresses resistance to infection e.g. immuno-suppression, chemotherapy, radiation, long term or recent hight dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection, e.g. leukemia, lymphoma, AIDS.

- ☐ **Other**

Appendix D
Anemia and Blood Transfusion Practices in the Critically Ill: A Prospective Observational Study

INFORMATION SHEET

Investigator: Jissy Thomas RN, MN (candidate)
(780) 407-8512 pager number: 445-3405
Supervisor: Dr. Louise Jensen, RN, PhD
(780) 492-6795

If you are consenting on behalf of a third party, 'you' should be read as 'your relative'.

INTRODUCTION:
You have been admitted to the General Systems Intensive Care Unit of the University of Alberta Hospital. During your stay in the ICU, you will require blood draws to help diagnose your disease, to monitor how you respond to treatment, and to provide information to help us treat you. You may also receive a blood transfusion if your doctor thinks it is necessary. You are urged to discuss any questions that arise about this study with the investigator who explains it to you.

PURPOSE:
The purpose of this study is to determine the volume of blood loss through blood draws, the rate of anemia, and the blood transfusion practices in critically ill patients such as you. It is hoped that the findings of this study will allow us to develop ways to reduce blood loss, manage anemia, and tell us more about blood-test and blood-unit ordering habits. We may also learn better ways of treating patients.

PROCEDURES:
We will collect information such as age, gender, reason for your admission to the ICU, date of admission to the ICU, APACHE II score (a point based score to assess severity of disease), date of discharge from the ICU, other medical history, number of blood draws, number of blood transfusions, number of blood units transfused, blood hemoglobin level at admission, and blood hemoglobin level prior to transfusion, from your chart. The bedside nurse involved in your care will assist in documenting part of the above information. Your doctor will be told that you are participating in this study.

BENEFITS:
There are no direct medical benefits for participating in this study. What we learn may be used to develop anemia management strategies in the future.

RISKS:
There will be no adverse effects or risks associated with participating in this study. Only information documented on your hospital chart will be obtained. If you decide not to participate in this study, you will receive the standard medical/nursing care that is normally given for your medical condition, which includes drawing blood for diagnostic purposes, and transfusing blood, as deemed clinically necessary by your physician.

COMPENSATION:
No payment or compensation will be made to you for participating in this study.

CONFIDENTIALITY:
Your identity will be kept confidential, and will be identified only by a number on the study records. The list with names and corresponding numbers will be kept under lock in the investigator's office, accessible to the investigator only. No subjects will be identified in any report or publication of this study and its results. By signing this consent form, you give permission to the study staff to access personally identifiable health information which is under the custody of other health care professionals as deemed necessary for the conduct of this research.

CONTACT PERSONS:
You may contact the principal researcher, Jissy Thomas at (780) 407-8512, or her supervisor Dr. Louise Jensen at (780) 492-6795 should you have any questions and/or concerns about this study. If you have any concerns and/or questions concerning your rights as a patient in an investigational study, you may contact the Patient Relations Office at (780) 407-1040.

Printed name of patient/family member:_____

Signature of patient/family member:_____

Printed name of investigator:_____

Signature of investigator:_____

DATE:_____

Appendix E

APACHE II Score Calculation*

(Acute Physiology And Chronic Health Evaluation)

Temperature (°C) 0	**Mean Arterial Pressure (mmHg)** 0	**Heart Rate** 0
Respiratory Rate 0	**If FIO2 >= 0,5 : (A-a) O2** 0	**If FIO2 < 0,5 : PaO2** 0
If no A.B.Gs : Serum HCO_3^- (mmol/L) 0	**Arterial pH** 0	**Serum Sodium (mmol/L)** 0
Serum Potassium (mmol/L) 0	**Serum Creatinine** With Acute Renal Failure 0	**Serum Creatinine** Without Acute Renal Failure 0
Ht (%) 0	**W.B.C ($x10^3$/ mm^3)** 0	**Glasgow Coma Score** 0
Age 0	**Apache II** 0 Clear	**Chronic Organ Insufficiency immuno-compromised** 0

* Adapted from the web page by Jean-Yves Marandon, MD and John C. Pezzullo, PhD, Associate Professor, Pharmacology and Biostatistics, Georgetown University Medical Center (USA).